REMARKS

The Amendments

The claims are amended to remove the "hydrate" terms and thus address the rejection based thereon. Claim 9 is amended to depend from claim 1 instead of claim 8 but is directed to the same subject matter. New dependent claim 14, supported, for example, by the disclosure at page 16 of the specification, is added as discussed below.

It is submitted that the above amendments would put the application in condition for allowance or materially reduce or simplify the issues for appeal. The amendments do not raise new issues or present new matter. One further dependent claims is added, however, the reasoning for its addition as a possible means for expediting prosecution here is discussed below. The amendments have been made to remove at least one rejection and direct the claims to subject matter which appears may be allowable. Thus, they were not earlier presented. Accordingly, it is submitted that the requested amendments should be entered.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The First Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 8 and 9 under 35 U.S.C. §112, first paragraph, for lack of enablement, is respectfully traversed.

It is believed that the above amendments may render the rejection moot. The statement of

the rejection appears to indicate that the non-enablement arises because of the term "improving" the impairment rather than treating the impairment. Accordingly, the method of use claims have been amended to recite "treating" the impairment. It appears that the amendment may remove the rejection. Further substantive support for enablement of the method of use claims is provided below. Additionally, applicants note that claim 9 and new claim 14 provide more specific method of use claims. Claim 9 has been written to depend on claim 1 and new claim 14 is provided dependent on claim 1. In the event that claim 8 is still considered non-enabled, the Examiner is encouraged to contact the undersigned to discuss the possibility of reverting to the subject matter of one of these claims.

Regardless of the above comment, it is urged that applicants' specification provides sufficient guidance for one of ordinary skill in the art to carry out the claimed methods. For example, at pages 17-22, applicants' specification provides several assays or tests from which the activity of the compounds pertinent to the claimed uses are shown or can be tested to be shown. An assay for PDE inhibition is disclosed at pages 17-19 of applicants' specification. An assay for intracellular neuronal cGMP concentration in cell cultures is disclosed at pages 19-20 of applicants' specification. An assay for long term potentiation is disclosed at pages 20-21 of applicants' specification, and a social recognition test is disclosed at pages 21-22 of applicants' specification.

One of ordinary skill in the art would have a reasonable expectation that compounds having such activity would be useful in methods for treating an impairment of learning and/or memory. As generally known, the glutamatergic system in the brain is deeply involved in learning and memory processes in the hippocampus and cortex of rodents, but also of primates

and humans. This can be proven by the memory deficits which are induced by systemic administration of NMDA-receptor antagonists (a specific glutamate receptor), such as phencyclidine, MK-801 or ketamine. Compounds which are able to facilitate glutamatergic neurotransmission can therefore enhance cognitive processes in diseases which have a dysfunction of the glutamatergic system. The learning and/or memory impairments – such as associated with Alzheimer's Disease and the other causes described in the specification – are related to such dysfunctional glutamatergic neurotransmission in the brain; see, e.g., the attached articles of Francis et al., *Int. J. Geriatric Psych.*, vol. 18, S15-21 (2003); and Francis et al., J.Neurochem., vol. 60, no. 5, pp. 1589-1604 (1993). The postsynaptic glutamatergic processes are linked to the NO/cGMP/cGK/CREB pathway which is involved in synaptic plasticity and learning and memory processes on a molecular level; see, e.g., Puzzo et al., cited above. Therefore, compounds enhancing cGMP levels in glutamatergic neurons, such as PDE9-inhibitors, are able to treat impairments of cognitive processes of memory deficits linked to a dysfunctional glutamatergic system, in general. The advantageous activity of the compounds for such use is not dependent on the cause of the impairment due to this general effect. The properties of PDE9-inhibitors for treating learning and/or memory impairments are shown by long-term potentiation experiments in-vitro and efficacy in the social recognition test in-vivo. Both, test paradigms are shown to be dependent on functional glutamatergic and/or NO/cGMP/cGK/CREB systems; see, e.g., attached Reymann et al., Neuropharmacology, vol. 52, pp. 24-40 (2007); and Puzzo et al., *J. Neurosci.*, vol. 25(29), pp. 6887-6897 (2005). Taken together, compounds like PDE9-inhibitors showing efficacy in the mentioned test paradigms (i.e. long-term potentiation and social recognition test) are likely be of therapeutic benefit for treating

learning and/or memory impairments linked to a dysfunctional glutamatergic system, as described by the current invention. In summary, therefore, there is a nexus between the type of physiological activity shown for the compounds (or readily verified by the assays provided in the specification) and the use for treating learning and/or memory impairments.

Additionally, applicants' comments on the Wands factors discussed in the Office action:

- Amount of Guidance – Applicants disagree with the allegation that they provided no guidance for carrying out the invention. As pointed out above, applicants point to the physiological activity and assays for determining such activity which have a nexus to use in carrying out the claimed methods.
- Unpredictability in the Art – Applicants respectfully disagree that any invention related to medicine is so unpredictable that non-enablement presumed. No evidence is provided to support the PTO's allegation of unpredictability here. Further, the standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).
- Number of Working Examples – The results of the assay at pages 17-19 showing PDE9A-inhibiting effect for the compounds of the invention are working examples. The results of the three following assays at pages 19-22 are also working examples of the physiological effect which has a nexus to use in carrying out the claimed methods.
- Nature of the Invention – The nature of the invention, as stated in the Office action, provides no implication of non-enablement.
- State of the Prior Art – The novelty of the invention (as indicated by the statement in the Office action) does not create any presumption of non-enablement. In order to support a

rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, the burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971). No such proof has been provided to support that the compounds would not be useful in the claimed methods.

- Level of Skill in the Art – Applicants strongly disagree that the level of skill of one of ordinary skill in this art is low. The level of skill is not an assessment of what has been accomplished in the effort, as asserted in the Office action. It is the level of the skill of those in the art working to solve the problem. That, historically, the disease or condition has been difficult to treat is not indicative of a low level of skill. To the contrary, the difficulty of treating the disease or condition – and the high impact of finding a treatment – means that those of very high skill level are working on the solution. Those working to find treatments as stated in the instant claims are Ph.D. level researchers at the highest level.
- Breadth of the Claims – The breadth of the claims is not addressed in the Office action but the breadth of claims here supports a finding of enablement. The compounds used for the methods are very well characterized and of a specific scope.
- Amount of Experimentation – The amount of experimentation required is not addressed in the Office action. However, even if some further experimentation is required, such does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the

art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., In re Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."

For all of the above reasons, it is urged that one of ordinary skill in the art is adequately taught by applicants' specification – taken in view of the knowledge of one of ordinary skill in the art – how to carry out the claimed invention. Thus, the claims are enabled and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Second Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 1-5, 7 and 13 under 35 U.S.C. §112, first paragraph, for lack of enablement, is rendered moot by the above amendments. The "hydrate" terms are removed from the claims. Applicants remain of the opinion that providing hydrates would not require undue

experimentation and reserve the right to prosecute this subject matter in a continuing application. The claims are amended merely to facilitate prosecution by removing this ground of rejection.

The Provisional Obviousness-type Double Patenting Rejection

The provisional obviousness-type double patenting rejection of claims 8-10 over claims 1-3 of the copending application published as US 2006/0100222 is respectfully traversed.

There is no overlap between the currently claimed subject matter in this and the copending application. Note the amendment filed February 11, 2009, in the copending application published as US 2006/0100222. The compounds used in the methods of the current claims are distinguished from those used in the methods of the copending claims at least based on the group corresponding to R1 in the instant claims. The rejection should be withdrawn at least for this reason.

Further, in accordance with M.P.E.P. §804(I)(B)(1), "If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." The current application is the earlier-filed of the two applications and it is believed by the above amendments that it is otherwise in condition for allowance. Thus, the provisional rejection should be withdrawn in accordance with the PTO practice.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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